assessment of said labeled cells for alterations in at least one tumor diathesis-associated molecule.

(Original) 2. The method of claim 1, wherein as an intermediary step between step c) and step d) the sample is contacted with an agent that detectably labels hematopoietic cells.

(Original) 3. The method of claim 2 wherein said assessment of said tumor diathesis associated molecule comprises contacting said molecule with a detectably labeled agent having binding affinity for said molecule.

(Amended) 4. The method of claim 3, wherein said [ligand] EpCAM antibody is coupled to a first detectable label, said reagent is coupled to a second detectable label, said hematopoietic cells are labeled with a third detectable label and said tumor diathesis associated molecule is contacted with an agent coupled to a fourth detectable label, said first, second, third and fourth detectable labels being different.

(Original) 5. The method as claimed in claim 1, wherein said labeled malignant cells are analyzed by a process selected from the group consisting of multiparameter flow cytometry, immunofluorescent microscopy, laser scanning cytometry, bright field base image analysis, capillary volumetry, spectral imaging analysis manual cell analysis, Cell Spotter® analysis, Cell Tracks analysis and automated cell analysis.

(Original) 6. The method as claimed in claim 1, wherein said method is applied to detect and enumerate residual cancer cells in said biological specimen and said cells are further analyzed for alterations in at least one predetermined tumor diathesis-associated molecule following at least one tumor eradication procedure.

(Original) 7. The method as claimed in claim 1, wherein said biological specimen is obtained from said patient periodically and assessed for the presence and

number of circulating cancer cells and said cells are further analyzed for alterations in at least one predetermined tumor diathesis-associated molecule as an indicator of progression of said malignancy.

(Original) 8. The method as claimed in claim 1, wherein said labeled malignant cells are contacted with chemotherapeutic agents to assess sensitivity thereto.

(Amended) 9. The method as claimed in claim 1, wherein said sample is an immunomagnetic sample comprising said biological specimen mixed with magnetic particles coupled to said [ligand] EpCAM antibody and wherein as an intermediate step between preparation of said immunomagnetic sample and contacting said immunomagnetic sample with at least one reagent, said immunomagnetic sample is subjected to a magnetic field to produce an enriched malignant cell suspension as the immunomagnetic sample.

(Original) 10. The method as claimed in claim 9, wherein the volume of said immunomagnetic sample containing said enriched malignant cells is reduced relative to the volume of the original biological specimen.

(Original) 11. The method as claimed in claim 9, wherein said magnetic particles are colloidal.

(Amended) 12. The method as claimed in claim 9, wherein said [ligand] EpCAM antibody is a monoclonal antibody specific for at least one cancer cell determinant, and said at least one reagent comprises at least one additional monoclonal antibody specific for a second cancer cell determinant and a third monoclonal antibody specific for an antigen present on a non tumor-cell, and said method further comprises adding to said labeled cancer cell-containing fraction a cell specific dye to allow exclusion of residual non-nucleated cells and cell debris from analysis.

(Cancel) 13. The method as claimed in claim 12, wherein said ligand binds specifically to an epithelial cell adhesion molecule on said malignant cell.

(Original) 14. The method as claimed in claim 12, wherein said one or more reagent binds specifically to an intracellular cytokeratin.

(Original) 15. The method of claim 1, wherein said tumor diathesis-associated molecule is at least one of the molecules set forth in Table XII.

(Original) 16. The method of claim 1, wherein said altered tumor diathesis-associated molecules are proteins present on individual cells and are assessed by a method selected from the group consisting of Cell Spotter® cytometry, Cell Tracks cytometry, immunofluorescence, mass spectometry and flow cytometry.

(Original) 17. The method of claim 1, further comprising isolation and culturing of malignant cells isolated from said biological specimen.

(Original) 18. The method of claim 17, wherein said cultured malignant cells are expanded from single cell colonies to generate clonal populations of said malignant cells.

(Original) 19. The method of claim 18, wherein said clonal populations of cells are assessed for alterations in tumor diathesis associated molecules.

(Original) 20. A malignant cell isolated from the cultured cells obtained from the method of claim 17.

(Original) 21. A tumor vaccine comprising a cell, or a component thereof, as claimed in claim 20.

(Original) 22. An altered diathesis associated molecule isolated from the cells of claim 19.

(Original) 23. A tumor vaccine comprising the altered diathesis molecule of claim 19 or a fragment thereof.

(Original) 24. The method of claim 17, further comprising contacting the cells with a therapeutic agent to assess sensitivity thereto.

(Original) 25. The method of claim 22, wherein proteinaceous tumor diathesis-associated molecules present in said cultured cells are analyzed by a method selected from the group consisting of protein gel electrophoresis, column chromatography, HPLC, FPLC, immunohistochemistry, histochemistry and western blotting.

(Original) 26. The method of claim 1, wherein said altered tumor diathesis-associated molecules are nucleic acids and are assessed by at least one method selected from the group consisting of library amplification of nucleic acids, polymerase chain reaction, agarose gel electrophoresis, Southern blotting, and Northern blotting.

(Original) 27. The method of claim 26, wherein said library amplification is performed on genetic material isolated from an individual cell and said amplified genetic material is subjected to gene specific probing.

(Original) 28. The method of claim 26 wherein said library amplification is performed on genetic material isolated from a plurality of malignant cells and said amplified genetic material is subjected to gene specific probing.

(Amended) 29. A method for assessing a patient for the presence of a non-hematopoietic malignancy, comprising:

a) obtaining a biological specimen from a patient, said specimen comprising a mixed cell population comprising hematopoietic and non-hematopoietic malignant cells;

b) preparing an immunomagnetic sample wherein said biological specimen is mixed with magnetic particles coupled to a [ligand] <u>EpCAM antibody</u> which reacts specifically with the malignant cells, to the substantial exclusion of other sample components;

c) separating said magnetic particle containing malignant cells from non-magnetic particle hematopoietic cells, and

d) analyzing said magnetic particle-containing cells to determine the presence and number of any malignant cells in said sample, detection of said cells indicating the presence of malignancy, the greater the number of cells present, the greater the severity of the malignancy; wherein the method further comprises assessment of said magnetic particle containing malignant cells for alterations in tumor diathesis-associated cellular molecules.

(Original) 30. The method of claim 29, wherein said altered tumor diathesis-associated molecules are nucleic acids and are assessed by at least one method selected from the group consisting of library amplification of nucleic acids, polymerase chain reaction, agarose gel electrophoresis, Southern blotting, and Northern blotting.

(Original) 31. The method of claim 30, wherein said library amplification is performed on genetic material isolated from an individual cell and said amplified genetic material is subjected to gene specific probing.

(Original) 32. The method of claim 30 wherein said library amplification is performed on genetic material isolated from all malignant cells isolated and said amplified genetic material is subjected to gene specific probing.

(Original) 33. The method of claim 1, wherein said altered tumor diathesis-associated molecules are carbohydrates and are assessed by a method selected from the group consisting of mass spectometry, lectin chromatography, and boronate affinity.

(Original) 34. The method as claimed in claim 1, wherein said patient has been diagnosed with an epithelial cell carcinoma selected from the group consisting of prostate cancer, breast cancer, colon cancer, bladder cancer, ovarian cancer, renal cancer, head and neck cancer, pancreatic cancer and lung cancer.

(Original) 35. The method of claim 34, wherein labeled cells are assessed for alterations in tumor diathesis-associated molecules selected from the group consisting of estrogen receptor, progesterone receptor, Her2/neu and MUC1.

(Original) 36. The method of claim 34, wherein said labeled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of androgen receptor, PSA, uPA and PSMA.

(Original) 37. The method of claim 34, wherein said labeled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of thymidylate synthase, EGFR, MUC2 and CEA-15.

(Original) 38. The method of claim 34, wherein said labelled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of CEA-19-3, HCG, MDR, and MUC1.

(Original) 39. The method of claim 34, wherein said labeled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of thymidylate synthase, MDR, Her-2/neu, and EGFR.

(Original) 40. The method of claim 1, wherein said patient has stage I cancer.

(Original) 42. The method of claim 1, wherein said patient has stage II cancer.

(Original) 43. The method of claim 1, wherein said patient has stage III cancer.

(Original) 44. The method of claim 1, wherein said patient has stage IV cancer.

(Original) 45. The method as claimed in claim 29, wherein said patient has been diagnosed with an epithelial-derived cell carcinoma selected from the group consisting of prostate cancer, breast cancer, colon cancer, bladder cancer, ovarian cancer, renal cancer, head and neck cancer, pancreatic cancer and lung cancer.

(Original) 46. The method of claim 45, wherein labeled cells are assessed for alterations in tumor diathesis-associated molecules selected from the group consisting of estrogen receptor, progesterone receptor, Her2/neu and MUC1.

(Original) 47. The method of claim 45, wherein said labeled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of androgen receptor, PSA, uPA and PSMA.

(Original) 48. The method of claim 45, wherein said labeled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of thymidylate synthase, EGFR, MUC2 and CEA-15.

(Original) 49. The method of claim 45, wherein said labelled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of CEA-19-3, HCG, MDR, and MUC1.

(Original) 50. The method of claim 45, wherein said labeled cells are assessed for alterations in tumor diathesis associated molecules selected from the group consisting of thymidylate synthase, MDR, Her-2/neu, and EGFR.

(Original) 51. The method of claim 29, wherein said patient has stage I cancer.

(Original) 52. The method of claim 29, wherein said patient has stage II cancer.

(Original) 53. The method of claim 29, wherein said patient has stage III cancer.

(Original) 54. The method of claim 29, wherein said patient has stage IV cancer.

(Amended) 55. A method for determining alterations in tumor diathesis associated molecules as a means to predict efficacy of therapy, comprising:

a) obtaining a [sample] <u>specimen</u> from a patient;

b) <u>preparing an immunomagnetic sample wherein said specimen is mixed with magnetic particles coupled to an EpCAM antibody which reacts</u>

specifically with malignant cells, to the substantial exclusion of other sample components;

c) isolating and enumerating said circulating malignant cells from said sample if present, said method further comprising; and

d) determining the number of at least one predetermined tumor diathesis associated molecule on individual cells present in said sample as a means to predict efficacy of therapy.

(Amended) 56. A method for determining alterations in tumor diathesis associated molecules as a means to assess appropriate dosage for therapy, comprising:

a) obtaining a [sample] specimen from a patient;

b) preparing an immunomagnetic sample wherein said specimen is mixed with magnetic particles coupled to an EpCAM antibody which reacts specifically with malignant cells, to the substantial exclusion of other sample components;

c) isolating and enumerating said circulating malignant cells from said sample if present, said method further comprising; and

d) determining the number of at least one predetermined tumor diathesis associated molecule on individual cells present in said sample as a means to assess appropriate dosage for therapy.

(Amended) 57. A method for determining alterations in tumor diathesis associated molecules as a means to monitor efficacy of therapy, comprising:

a) obtaining a [sample] specimen from a patient;

b) preparing an immunomagnetic sample wherein said specimen is mixed with magnetic particles coupled to an EpCAM antibody which reacts specifically with malignant cells, to the substantial exclusion of other sample components;

b) isolating and enumerating circulating malignant cells from said sample if present, said method further comprising; and

c) determining the number of at least one predetermined tumor diathesis associated molecule on individual cells present in said sample as a means to monitor efficacy of therapy.

(Original) 58. The method of claim 57, wherein said samples are obtained from said patient, before, during or after administration of a therapeutic agent.

(Original) 59. The method of claim 57, further comprising isolating and contacting said cells with a therapeutic agent to assess sensitivity thereto.

(Original) 60. The method of claim 55, wherein said patient has breast cancer and said tumor diathesis associated molecule is Her-2/neu and said therapy is administration of anti-Her-2/neu antibody or a fragment thereof.

(Original) 61. The method of claim 56, wherein said patient has breast cancer and said tumor diathesis associated molecule is Her-2/neu and said therapy is administration of anti-Her-2/neu antibody or a fragment thereof.

(Original) 62. The method of claim 57, wherein said patient has breast cancer and said tumor diathesis associated molecule is Her-2/neu and said therapy is administration of anti-Her-2/neu antibody or a fragment thereof.

(Original) 63. The method of claim 55, wherein said patient has breast cancer and said at least one tumor diathesis associated molecule comprises Her-2/neu and estrogen receptor and said therapy is administration of anti-Her-2/neu antibody or a fragment thereof and tamoxifen.

(Original) 64. The method of claim 56, wherein said patient has breast cancer and said at least one tumor diathesis associated molecule is Her-2/neu and estrogen receptor said therapy is administration of anti-Her-2/neu antibody or a fragment thereof and tamoxifen.

(Original) 65. The method of claim 57, wherein said patient has breast cancer and said at least one tumor diathesis associated molecule is Her-2/neu and

estrogen receptor and said therapy is administration of anti-Her-2/neu antibody or a fragment thereof and tamoxifen.

(Amended) 66. A method for determining alterations in tumor diathesis associated molecules as a means to assess cancer progression comprising:

a) obtaining a [sample] specimen from a patient;

b) preparing an immunomagnetic sample wherein said specimen is mixed with magnetic particles coupled to an EpCAM antibody which reacts specifically with malignant cells, to the substantial exclusion of other sample components;

c) isolating and enumerating circulating malignant cells from said sample if present, said method further comprising; and

d) determining whether said cells contain a predetermined tumor diathesis associated molecule associated with a poor prognosis as a means to assess cancer progression.

(Original) 67. The method of claim 66, wherein said tumor diathesis associated molecule is altered and is selected from the group consisting of Androgen Receptor, Cathepsin D, Estrogen Receptor, Estradiol, Progesterone Receptor, Somastatin, Steroid Receptor Coactivator-1 (SRC1), Her-2 (cERB-b), EGFR, ras, c-fos, c-jun, c-myc, p53, p63, nm23 / NDP Kinase, PTEN / MMAC1, SMAD4 / DPC4, Notch-1, JAK3, Cyclin A, Cyclin B, Cyclin C, Cyclin D, Cyclin E, Ki67, MDR/MRP proteins, PSA, Prostatic Acid Phosphatase, CA 125, CA 15-3, CA 27-29, HGC, Cystic Fibrosis Transmembrane Regulator, Laminin Receptor, Neuron Specific Enolase (NSE), Alpha Fetoprotein, CD99 /MIC2, DHEA, Prolactin, CD66e / CEA, Filaggrin, gp200, TAG72 / CA72-4, UPA-receptor (CD87), Heregulin, IPO-38, Thymidylate Synthase, Topoisomerase Iia, Glutathione-S-Transferase (GST), Lung-Resistance related Protein/Major Fault Protein (LRP/MFP), and 06-Methylguanine-DNA methyltransferase (MGMT).

(Original) 68. The method of claim 66, wherein said tumor diathesis associated molecule is aberrantly expressed relative to wild type expression and is selected

from the group consisting of Androgen Receptor, Cathepsin D, Estrogen Receptor, Estradiol, Progesterone Receptor, Somastatin, Steroid Receptor Coactivator-1 (SRC1), Her-2 (cERB-b), EGFR, ras, c-fos, c-jun, c-myc, p53, p63, nm23 / NDP Kinase, PTEN / MMAC1, SMAD4 / DPC4, Notch-1, JAK3, Cyclin A, Cyclin B, Cyclin C, Cyclin D, Cyclin E, Ki67, MDR/MRP proteins, PSA, Prostatic Acid Phosphatase, CA 125, CA 15-3, CA 27-29, HGC, Cystic Fibrosis Transmembrane Regulator, Laminin Receptor, Neuron Specific Enolase (NSE), Alpha Fetoprotein, CD99 /MIC2, DHEA, Prolactin, CD66e / CEA, Filaggrin, gp200 TAG72 / CA72-4, UPA-receptor (CD87), Heregulin, IPO-38 Thymidylate Synthase, Topoisomerase Iia, Glutathione-S- Transferase (GST), Lung-Resistance related Protein/Major Fault Protein (LRP/MFP), and 06-Methylguanine-DNA methyltransferase (MGMT).

(Original) 69. The method as claimed in claim 67, wherein said tumor diathesis associated molecule is a nucleic acid.

(Original) 70. The method as claimed in claim 68, wherein said tumor diathesis associated molecule is a nucleic acid.

(Original) 71. The method as claimed in claim 67, wherein said tumor diathesis associated molecule is a protein.

(Original) 72. The method as claimed in claim 68, wherein said tumor diathesis associated molecule is a protein.

(Amended) 73. A method for performing a whole body biopsy on a patient, comprising:

a) obtaining a blood [sample] <u>specimen</u> from a patient;

b) <u>preparing an immunomagnetic sample wherein said specimen is mixed with magnetic particles coupled to an EpCAM antibody which reacts specifically with malignant cells, to the substantial exclusion of other sample components;</u>

c) isolating and enumerating circulating non-hematopoietic malignant cells from said sample if present, said method further comprising; and

d) analyzing said cells for the presence and number of a panel of predetermined tumor diathesis associated molecules.

(Original) 74. The method of claim 73, wherein said tumor diathesis associated molecule comprises at least two molecules selected from the group consisting of Androgen Receptor, Cathepsin D, Estrogen Receptor, Estradiol, Progesterone Receptor, Somastatin, Steroid Receptor Coactivator-1 (SRC1), Her-2 (cERB-b), EGFR, ras, c-fos, c-jun, c-myc,p53, p63, nm23 / NDP Kinase, PTEN / MMAC1, SMAD4 / DPC4, Notch-1, JAK3, Cyclin A, Cyclin B, Cyclin C, Cyclin D, Cyclin E, Ki67, MDR/MRP proteins, PSA, Prostatic Acid Phosphatase, CA 125, CA 15-3, CA 27-29, HGC, Cystic Fibrosis Transmembrane Regulator, Laminin Receptor, Neuron Specific Enolase (NSE), Alpha Fetoprotein, CD99 /MIC2, DHEA, Prolactin, CD66e / CEA, Filaggrin, gp200, TAG72 / CA72-4, UPA-receptor (CD87), Heregulin, IPO-38, Thymidylate Synthase, Topoisomerase Iia, Glutathione-S- Transferase (GST), Lung-Resistance related Protein/Major Fault Protein (LRP/MFP), and 06-Methylguanine-DNA methyltransferase (MGMT).

(Original) 75. The method as claimed in claim 73, wherein said patient has an epithelial cell cancer selected from the group consisting of prostate cancer, breast cancer, colon cancer, bladder cancer, ovarian cancer, renal cancer, uterine cancer, head and neck cancer, pancreatic cancer and stomach cancer.

(Original) 76. A method for identifying alterations in a circulating tumor cell relative to the tumor mass in situ, comprising:

a) obtaining a biopsy specimen of said tumor mass from patient;

b) isolating circulating tumor cells from the serum of said patient, if present;

c) contacting said specimen and said isolated circulating tumor cells with a duplicate panel of agents which detect a plurality of tumor diathesis associated molecules;

d) detecting any tumor diathesis associated molecules present in said circulating tumor cells and in said specimen; and

e) determining whether said tumor diathesis associated molecules are altered in said circulating tumor cell relative to said biopsy specimen.

(Amended) 77. A test kit for screening a patient sample for the presence of a non-hematopoietic malignant cells comprising:

a) coated magnetic nanoparticles comprising a magnetic core material, a protein base coating material, and an EpCAM antibody that binds specifically to a first characteristic determinant of said malignant cell, said antibody being coupled, directly or indirectly, to said base coating material;

b) at least one antibody having binding specificity for a second characteristic determinant of said malignant cell;

c) a cell specific dye for excluding sample components other than said malignant cells from analysis;

d) a device selected from the group consisting of a Cell Spotter cartridge or a Cell Tracks cartridge; and

e) at least one detectably labeled agent having binding affinity for a tumor diathesis associated molecule.

(Original) 78. A kit as claimed in claim 48, said kit further containing an antibody which has binding affinity for non-target cells, a biological buffer, a permeabilization buffer, a protocol and optionally, an information sheet.

(Original) 79. A kit as claimed in claim 77 for screening patients for breast cancer, wherein said at least one detectably labeled agent having binding affinity for said tumor diathesis associated molecule is selected from the group consisting of MUC-1, estrogen, progesterone receptor, cathepsin D, p53, urokinase type plasminogen activator, epidermal growth factor, epidermal growth factor receptor, BRCA1, BRCA2, CA27.29, CA15.5, prostate specific antigen, plasminogen activator inhibitor and Her2-neu.

(Original) 80. A kit as claimed in claim 77 for screening patients for prostate cancer, wherein said at least one detectably labeled agent having binding affinity for said tumor diathesis associated molecule is selected from the group consisting of prostate specific antigen, prostatic acid phosphatase, thymosin b-15, p53, HPC1 basic prostate gene, creatine kinase and prostate specific membrane antigen.

(Original) 81. A kit as claimed in claim 77 for screening patients for colon cancer, wherein said at least one detectably labeled agent having binding affinity for said tumor diathesis associated molecule is selected from the group consisting of carcinoembryonic antigen, C protein, APC gene, p53, thymidylate synthase and matrix metalloproteinase (MMP-9).

(Original) 82. A kit as claimed in claim 77 for screening patients with bladder cancer, wherein said at least one wherein said at least one detectably labeled agent having binding affinity for said tumor diathesis associated molecule is selected from the group consisting of nuclear matrix protein (NMP22),Bard Bladder tumor antigen (BTA), and fibrin degradation product (FDP).

(Original) 83. A test kit as claimed in claim 77, wherein said at least one antibody comprises a panel of antibodies each having binding specificity for a different cancer cell characteristic determinant.